NDA 12-649/S-046

SEP 2 4 1999

Merck and Co., Inc.
Sunmeytown Pike
P.O. Box 4
West Point, PA 19486

Attention: Dennis M. Erb, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. Erb:

Please refer to your supplemental new drug application dated August 13, 1999, received August 16, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Periactin (cyproheptadine HCl) Tablets, 4 mg.

We note that this supplement was submitted as 'Special Supplement, Changes Being Effected' under 21 CFR 3 14.70(c).

This supplemental new drug application provides for deletion of information about Periactin Syrup, and revisions to the package insert accordingly. Your submission stated January 1, 2000, as the implementation date for these changes.

We have completed the review of this supplemental application, and have the editorial revisions listed below. Accordingly, this supplemental application is approved effective on the date of this letter.

Since the syrup formulation is no longer available, the following changes should be addressed in the Pharmacokinetics and Metabolism subsection of CLINICAL PHARMACOLOGY.

1. Remove "or syrup" from the sentence "After a single 4 mg oral dose of ^{14}C-labelled cyproheptadine HCl in normal subjects, given as tablets or syrup."

2. Remove the sentence "No significant difference in the mean urinary excretion exists between the tablet and syrup formulations."

3. Remove "of PERIACTIN Syrup" from the sentence "No detectable amounts of unchanged drug were present in the urine of patients on chronic 12-20 mg daily doses of PERIACTIN Syrup."

The final printed labeling (FPL) must be identical with the changes indicated, to the submitted draft labeling (package insert submitted August 13, 1999). These revisions are terms of the NDA supplement approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 12-649/S-046. Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Ms. Ladan Jafari, Project Manager, at (301) 827-5584.

Sincerely,

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

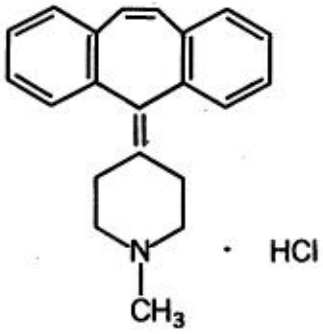
MERCK & CO., INC.
West Point, PA 19486, USA

TABLETS
PERIACTIN®
(CYPROHEPTADINE HCl)

DESCRIPTION

PERIACTIN (Cyproheptadine HCl) is an antihistaminic and antiserotonergic agent.

Cyproheptadine hydrochloride is a white to slightly yellowish, crystalline solid, with a molecular weight of 350.89, which is soluble in water, freely soluble in methanol, sparingly soluble in ethanol, soluble in chloroform, and practically insoluble in ether. It is the sesquihydrate of 4-(5*H*-dibenzo[*a,d,*]cyclohepten-5-ylidene)-1-methylpiperidine hydrochloride. The empirical formula of the anhydrous salt is $C_{21}H_{21}N \bullet HCl$ and the structural formula of the anhydrous salt is:



PERIACTIN is available in tablets, containing 4 mg of cyproheptadine hydrochloride.

The tablets also contain the following inactive ingredients: calcium phosphate, lactose, magnesium stearate, and starch.

CLINICAL PHARMACOLOGY

PERIACTIN is a serotonin and histamine antagonist with anticholinergic and sedative effects. Antiserotonin and antihistamine drugs appear to compete with serotonin and histamine, respectively, for receptor sites.

Pharmacokinetics and Metabolism

After a single 4 mg oral dose of ^{14}C-labelled cyproheptadine HCl in normal subjects, given as tablets or syrup, 2-20% of the radioactivity was excreted in the stools. Only about 34% of the stool radioactivity was unchanged drug, corresponding to less than 5.7% of the dose. At least 40% of the administered radioactivity was excreted in the urine. No significant difference in the—mean urinary excretion exists between the tablet and syrup formulations. No detectable amounts of unchanged drug were present in the urine of patients on chronic 12-20-mg daily doses PERIACTIN syrup. The principal metabolite found in human urine has been identified as a quaternary ammonium glucuronide conjugate of cyproheptadine. Elimination is diminished in renal insufficiency.

INDICATIONS AND USAGE

Perennial and seasonal allergic rhinitis
Vasomotor rhinitis
Allergic conjunctivitis due to inhalant allergens and foods
Mild, uncomplicated allergic skin manifestations of urticaria and angioedema
Amelioration of allergic reactions to blood or plasma
Cold urticaria
Dermatographism

As therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.

CONTRAINDICATIONS

Newborn or Premature Infants

This drug should not be used in newborn or premature infants.

Nursing Mothers

Because of the higher risk of antihistamines for infants generally and for newborns and prematures in particular, antihistamine therapy is contraindicated in nursing mothers.

Other Conditions

Hypersensitivity to cyproheptadine and other drugs of similar chemical structure:
Monoamine oxidase inhibitor therapy (see DRUG INTERACTIONS)
Angle-closure glaucoma
Stenosing peptic ulcer
Symptomatic prostatic hypertrophy
Bladder neck obstruction
Pyloroduodenal obstruction
Elderly, debilitated patients

WARNINGS

Pediatric Patients

Overdosage of antihistamines, particularly in infants and young children, may produce hallucinations, central nervous system depression, convulsions, and death.

Antihistamines may diminish mental alertness; conversely, particularly, in the young child, they may occasionally produce excitation.

CNS Depressants

Antihistamines may have additive effects with alcohol and other CNS depressants, e.g., hypnotics, sedatives, tranquilizers, antianxiety agents.

Activities Requiring Mental Alertness

Patients should be warned about engaging in activities requiring mental alertness and motor coordination, such as driving a car or operating machinery.

Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patient (see PRECAUTIONS, *Geriatric Use*)

PRECAUTIONS

General

Cyproheptadine has an atropine-like action and, therefore, should be used with caution in patients with:
History of bronchial asthma
Increased intraocular pressure
Hyperthyroidism
Cardiovascular disease
Hypertension

Information for Patients

Antihistamines may diminish mental alertness; conversely, particularly, in the young child, they may occasionally produce excitation.

Patients should be warned about engaging in activities requiring mental alertness and motor coordination, such as driving a car or operating machinery.

Drug Interactions

MAO inhibitors prolong and intensify the anticholinergic effects of antihistamines.

Antihistamines may have additive effects with alcohol and other CNS depressants, e.g., hypnotics, sedatives, tranquilizers, antianxiety agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenic studies have not been done with cyproheptadine.

Cyproheptadine had no effect on fertility in a two-litter study in rats or a two generation study in mice at about 10 times the human dose.

Cyproheptadine did not produce chromosome damage in human lymphocytes or fibroblasts in vitro high doses (10^{-4}M) were cytotoxic. Cyproheptadine did not have any mutagenic effect in the Ames microbial mutagen test; concentrations of above 500 mcg/plate inhibited bacterial growth.

Pregnancy

Pregnancy Category B: Reproduction studies have been performed in rabbits, mice, and rats at oral or subcutaneous doses up to 32 times the maximum recommended human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to cyproheptadine. Cyproheptadine has been shown to be fetotoxic in rats when given by intraperitoneal injection in doses four times the maximum recommended human oral dose. Two studies in pregnant women, however, have not shown that cyproheptadine increases the risk of abnormalities when administered during the first, second and third trimesters of pregnancy. No teratogenic effects were observed in any of the newborns. Nevertheless, because the studies in humans cannot rule out the possibility of harm, cyproheptadine should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from PERIACTIN, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother(see CONTRAINDICATIONS).

Pediatric Use

Safety and effectiveness in ediatric patients below the age of two have not been established. See CONTRAINDICATIONS, *Newborn or Premature Infants*, and WARNINGS, *Pediatric Patients*.

Geriatric Use

Clinical studies of PERIACTIN Tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see WARNINGS, *Activities Requiring Mental Alertness*).

ADVERSE REACTIONS

Adverse reactions which have been reported with the use of antihistamines are as follows:

Central Nervous System: Sedation and sleepiness (often transient), dizziness, disturbed coordination, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, paresthesias, neuritis, convulsions, euphoria, hallucinations, hysteria, faintness.

Integumentary: Allergic manifestation of rash and edema, excessive perspiration, urticaria, photosensitivity.

Special Senses: Acute labyrinthitis, blurred vision, diplopia, vertigo, tinnitus.

Cardiovascular: Hypotension, palpitation, tachycardia, extrasystoles, anaphylactic shock.

Hematologic: Hemolytic anemia, leukopenia, agranulocytosis, thrombocytopenia.

Digestive System: Cholestasis, hepatic failure, hepatitis, hepatic function abnormality, dryness of mouth, epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation, jaundice.

Genitourinary: Urinary frequency, difficult urination, urinary retention, early menses.

Respiratory: Dryness of nose and throat, thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.

Miscellaneous: Fatigue, chills, headache, increased appetite/weight gain.

OVERDOSAGE

Antihistamine overdosage reactions may vary from central nervous system depression to stimulation especially in pediatric patients Also, atropine-like signs and symptoms (dry mouth; fixed, dilated pupils; flushing, etc.) as well as gastrointestinal symptoms may occur.

If vomiting has not occurred spontaneously the patient should be induced to vomit with syrup of ipecac.

If the patient is unable to vomit, perform gastric lavage followed by activated charcoal. Isotonic or ½ isotonic saline is the lavage of choice. Precautions against aspiration must be taken especially in infants and children.

When life threatening CNS signs and symptoms are present, intravenous physostigmine salicylate may be considered. Dosage and frequency of administration are dependent on age, clinical response, and recurrence after response. (See package circulars for physostigmine products.)

Saline cathartics, as milk of magnesia, by osmosis draw water into the bowel and, therefore, are valuable for their action in rapid dilution of bowel content.

Stimulants should *not* be used.

Vasopressors may be used to treat hypotension.

The oral LD_{50} of cyproheptadine is 123 mg/kg, and 295 mg/kg in the mouse and rat, respectively.

DOSAGE AND ADMINISTRATION

DOSAGE SHOULD BE INDIVIDUALIZED ACCORDING TO THE NEEDS AND THE RESPONSE OF THE PATIENT.

Each PERIACTIN tablet contains 4 mg of cyproheptadine hydrochloride.

Pediatric Patients

Age 2 to 6 years

The total daily dosage for pediatric patients may be calculated on the basis of body weight or body area using approximately 0.25 mg/kg/day or 8 mg per square meter of body surface (8 mg/m^2).

The usual dose is 2 mg (1/2 tablet) two or three times a day, adjusted as necessary to the size and response of the patient. The dose is not to exceed 12 mg a day.

Age 7 to 14 years

The usual dose is 4 mg (1 tablet) two or three times a day, adjusted as necessary to the size and response of the patient. The dose is not to exceed 16 mg a day.

Adults

The total daily dose for adults should not exceed 0.5 mg/kg/day.

The therapeutic range is 4 to 20 mg a day, with the majority of patients requiring 12 to 16 mg a day. An occasional patient may require as much as 32 mg a day for adequate relief. It is suggested that dosage be initiated with 4 mg (1 tablet) three times a day and adjusted according to the size and response of the patient.

HOW SUPPLIED

No. 3276 — Tablets PERIACTIN, containing 4 mg of cyproheptadine hydrochloride each, are white, round, scored, compressed tablets, coded MSD 62 on one side and PERIACTIN on the other. They are supplied as follows:

NDC 0006-0062-68 bottles of 100

(6505-00-890-1884 4 mg 100's).

Storage

Store Tablets PERIACTIN at controlled room temperature, 15 - 30°C (59 - 86°F), in a well-closed container.

Dist.by:
MERCK & CO., INC., West Point, PA 19486, USA
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